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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/662,183	09/12/2003	Serge Auvin	427.044-DIV	9445

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EXAMINER	
MURRAY, JEFFREY H	

ART UNIT	PAPER NUMBER
1609	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/662,183	AUVIN ET AL.	
	Examiner	Art Unit	
	Jeffrey H. Murray	1609	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-25* is/are pending in the application.

4a) Of the above claim(s) *21-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 14-25 are pending and are examined herein.

Election/Restrictions

1. Applicant's election of Group I in Paper No. 18 on 4/10/2007 is acknowledged. Applicant has made the election and amended the claims to encompass elected subject matter. The election is being treated as an election with traverse. Claims 1-13 have been cancelled, and Claims 21-25 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Claims 14-20 will be examined herein.

Examiner admits a typographical error within the restriction in regards to the Claim numbering. Claim 21-25 should be removed from Groups I-VII and Claims 21-25 should be the only Claims in Groups VIII-XIV. This is merely to separate compound Claims from the method of use Claims. Examiner wishes to remind applicant that upon searching Group I of the restriction requirement, if claims are found to be allowable concerning the compounds, the method claims will be permitted to be rejoined in the search.

In response to applicant's traverse, the request for an election of a species is used merely as a starting point for the examiner's search. If Example 57 is found to be allowable subject matter, then additional compounds from Group I will be selected and will be searched for patentability.

Priority

2. Claims 14-25 are given a priority date of September 23, 1998. This application is a domestic application 10/662,183, filed September 12, 2003, which is a divisional of application

09/787,467, filed March 16, 2001, which is a national stage entry of PCT/FR99/02250, filed September 22, 1999, which claims the benefit of foreign priority to application FR 9811868, filed September 23, 1998.

Specification

3. The disclosure is objected to because of the following informalities:

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections **in order**. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.
(e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.
(f) BACKGROUND OF THE INVENTION.
    (1) Field of the Invention.
    (2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(g) BRIEF SUMMARY OF THE INVENTION.
(h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(i) DETAILED DESCRIPTION OF THE INVENTION.
(j) CLAIM OR CLAIMS (commencing on a separate sheet).
(k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

Appropriate correction is required.

4. The disclosure is objected to because of the following informalities:

5. Throughout the "PREPARATION OF THE COMPOUNDS OF THE INVENTION" section in the specification, a "general formula V" is discussed whereby "general formula V" takes on many connotations. On page 37, Diagram 4 shows general formula V whereby X is a carboxamide and Y and Φ can be anything. However, on page 43, general formula V is perceived as both a carboxamide and a reverse carboxamide where X is or is not a bond. Clarification of general formula V is recommended by adding subtitles such as formula V_1 or formula V_2 for example to denote the fact that while these structures fall into the "general formula V" they are each distinct and different compounds with varying amide, reverse amide, ether, etc. linkages. Appropriate correction is required.

6. Line 8 of the specification reads, "radical in which R_1, R_2, and R_3 represent, independently, a halogen, the OH or SR_6" "The" is used in patent Claim language to refer back to a specific item from a previous Claim. "The OH" can be interpreted as referring back to a specific OH group, none of which is aforementioned in the specification. Examiner suggests changing the phrase to "an OH group" for clarity. This phrase is used repeatedly later in the specification (page 4, line 1 and line 13; page 5, line 7; page 11, line 6 and line 15; page 12, line 1; page 25, line 9; page 26, line 1 and line 13. Appropriate correction is required.

7. On page 3, line 8 of the specification reads, "radical in which R_1, R_2, and R_3 represent, independently, a halogen, the OH or SR_6" "The OH" can be interpreted as referring back to a specific OH group, none of which is aforementioned in the specification. Examiner suggests changing the phrase to "an OH group" for clarity. This phrase is used repeatedly later in the

specification (page 4, line 1 and line 13; page 5, line 7; page 11, line 6 and line 15; page 12, line 1; page 25, line 9; page 26, line 1 and line 13. Appropriate correction is required.

8. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any of the errors of which applicant may become aware of in the specification. Introduction of New Matter must be avoided.

Claim Objections

9. Claim 15 objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

10. Claim 15 is objected to because of the following informalities: Claim 15, line 28, reads, "R_{36} and R_{37} are independently selected from....". However due to the claim limitation of Φ in line 26, there is no R_{37} present in the compound of Claim 15. Appropriate correction is required.

11. Claim 15 objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 15 in its last line claims, "and a salt thereof." Claim 15 is a dependent claim which refers back to Claim 14. Claim 14 in its last line claims, "and its pharmaceutically acceptable salts." Due to Claim 15 not clarifying this point, Claim 15 can be construed to mean either a

"pharmaceutically acceptable salt" such as those in Claim 14, or a non-pharmaceutically acceptable salt. This is broadening and is not permitted. Appropriate correction is required.

Claim Rejections - 35 USC § 112

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 14-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation. (United States v. Teletronics Inc., 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors (See Ex parte Forman 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988).

These factors include the following:

1) Amount of guidance provided by applicant.

2) Unpredictability in the art.

3) Number of working examples.

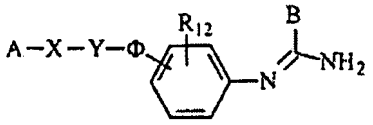
4) Scope of the claims.

5) Nature of the invention.

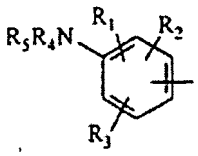
6) Level of skill in the art.

1) *Amount of guidance provided by Applicant.* While the Applicant has demonstrated within the application how to make a select number of amidine derivatives to be used as NO synthase or lipidic peroxidation inhibitors, the generic Claim 1 is massive. While over eighty compounds have been synthesized, only a small fraction (14) of these compounds fall into Group I, are discussed, and their syntheses shown. For example, no working examples exist that show these compounds could e used on humans as NO synthase inhibitors. No evidence from prior art has been shown nor any current evidence shown that might explain why these compounds can and would be used as NO synthase inhibitors.

In the specification, page 32 begins to describe the processes for assembling the various core structures in this application, using multiple diagrams to synthesize the amidine derivatives. The specification goes into detail on how to build a compound with the following features: From the general formula I':



where A is



However, the specification does not describe in detail all of the possibilities that are encompassed by the broad Claim 14. Claim 14 describes X, Y and O as numerous different linkers, bonds and connecting atoms. Y even has the possibility of containing a heterocyclic ring moiety. The specification only demonstrates and describes in detail a small number of these possible linkers. No explanation has been made within the specification on whether where X is concerned in Claim 14, X may be a number of different linkers such as, but not limited to: an alkyl, alkyl ketone, ether, sulfide, amino, amide, alkene or imine. The specification only demonstrates a small number of these examples leaving many of the possibilities for X undisclosed. The same holds true for the Φ variable. No reference is made as to how to synthesize any of these other compound combinations which are claimed in the present application and one of ordinary skill in the art would not have the common knowledge on how to synthesize this compound. The specification only demonstrates a small number of these examples leaving a large number of the possible compounds undisclosed, and hence not enabled.

Of those that are enabled, the synthetic scheme that applicant has provided for the synthesis of these types of compounds is not necessarily a viable method considering all the variables involved. For example, the specification describes a procedure for synthesizing these compounds with a method for synthesizing the final compound precursor, involving Pd/C, H_2, and Ethanol as a solvent:

However, according to Claim 1, X may be –CH=CH or –CH=N. Both of these groups could very likely be reduced from a Pd/C/hydrogenation reduction reaction. (King et. al. page 2-

3) Likewise, benzylic esters and ethers, both of which may exist under the broad and various Markush groups for X, Y and Φ allowed in Claim 1, would be reduced or reacted with under these conditions. (King et. al. page 5)

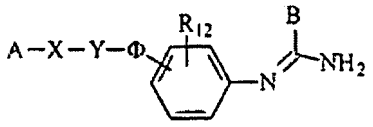
2) *Unpredictability in the art.* It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. (USPQ 18, 24 (CCPA 1970). See *In re Fisher*, 427 F.2d 833, 839, 166.

Nitric oxide synthase is a good example. Within the body, nitric oxide is a necessity and has been identified as an important signaling molecule in almost every tissue in the body. (Koti et. al. p.391, col.2 para.2). Here applicants wish to use desired compounds as a potential NO synthase inhibitor. However, applicant has not addressed the fact that NO synthase is involved in multiple aspects and pathways in the human body. For example, treatment of rats with nonspecific NO synthase inhibitors resulted in a failure of microvascular perfusion and development of patchy necrosis. (Koti et. al. p.391, col.2 para.2) The underproduction or overproduction of nitric oxide (NO) in the body has also been shown to lead to a variety of eye diseases. (Chiou et. al. p. 189). In another instance, when the NO pathway is blocked, it is reported that levels are lowered within the body, and hence lowered in the brain. When this occurs there is an increased risk of "chaotic cerebral vasomotion" which can eventually lead to a stroke. (Lacza et. al. p.263, col.2 para.4). This is just a sample of possible unpredictable side effects that may result from the inhibiting of a NO synthase enzyme.

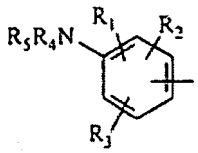
3) *Number of working examples.* Applicant has provided over 80 working example compounds however only approximately 14 of these claimed compounds fall under the Group I

election in the present application. This is a miniscule fraction of the number of compounds that exist in the broad Claim 1.

4) *Scope of the claims.* The scope of the claims involve all of the thousands of compounds of general formula I':



where A is



Thus, the scope of claims is very broad.

5) *Nature of the invention.* The nature of this invention relates generally to phenyl amidine compounds and methods of using the same which are considered NO-synthase inhibitor and lipidic peroxidation inhibitor compounds.

6) *Level of skill in the art.* The artisan making Applicants invention would be a chemist with several years experience. The artisan using Applicant's invention would be a physician with a M.D. degree, and having several years of experience.

MPEP §2164.01 (a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27

USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here that Applicant is not enabled for making these compounds or compositions or treating the diseases mentioned.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 14-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Aslam, et. al. Pakistan Journal of Pharmacy 1995 8(2), 9-22, *17*. The instantly claimed compounds read on the reference compound. See STN search for CAS registry number 191932-53-3, i.e., the corresponding R_{18}, R_{19}, R_{20}, R_{21}, R_{22} and R_{39} are hydrogen, B is NH_2, X is $-(CH_2)_m-C(O)$, Y is a bond, and Φ is $-(CH_2)_m-O-(CH_2)_n$, where m and n are 0.

Conclusion

16. Claims 14-20 are rejected.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey H. Murray whose telephone number is 571-272-9023. The examiner can normally be reached on M-F 7:30-5pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisors, Cecilia Tsang can be reached at 571-272-0562 or Janet Andres can be reached at

571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jeffrey H. Murray

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER